



Biokinetics of Nuclear Fuel Compounds and Biological Effects of Nonuniform Radiation

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Environmental releases of insoluble nuclear fuel compounds may occur at nuclear power plants during normal operation, after nuclear power plant accidents, and as a consequence of nuclear weapons testing. For example, the Chernobyl fallout contained extensive amounts of pulverized nuclear fuel composed of uranium and its nonvolatile fission products. The effects of these highly radioactive particles, also called hot particles, on humans are not well known due to lack of reliable data on the extent of the exposure. However, the biokinetics and biological effects of nuclear fuel compounds have been investigated in a number of experimental studies using various cellular systems and laboratory animals. In this article, we review the biokinetic properties and effects of insoluble nuclear fuel compounds, with special reference to UO_2 , PuO_2 , and nonvolatile, long-lived β -emitters Zr, Nb, Ru, and Ce. First, the data on hot particles, including sources, dosimetry, and human exposure are discussed. Second, the biokinetics of insoluble nuclear fuel compounds in the gastrointestinal tract and respiratory tract are reviewed. Finally, short- and long-term biological effects of nonuniform α - and β -irradiation on the gastrointestinal tract, lungs, and skin are discussed. **Key words:** biokinetics, cancer, hot particles, ionizing radiation, nuclear fission. *Environ Health Perspect* 103:920–934 (1995)

Exposure to radioactive particles made up of radionuclides from fission or activation reactions and/or actinides with activities up to millions of becquerels, also called hot particles, has been identified as an important radiological health problem in the nuclear power industry. For example, the Chernobyl nuclear power plant accident caused extensive global radioactive fallout which exposed millions of people to both volatile and nonvolatile radionuclides. It has been estimated that the fallout exposed the population of Europe to a dose of 0.2 mSv in the first year (1); the worldwide, average, annual effective dose from natural sources is estimated to be 2.4 mSv (2). However, approximate global dose estimates can never predict health effects of radioactive fallout composed of several radionuclides with different physicochemical properties. The Chernobyl fallout had a special feature, different from the earlier observed nuclear reactor accidents: it contained extensive amounts of pulverized nuclear fuel from the reactor which first exploded and then burned for several days. The nuclear fuel particles were composed of uranium and its nonvolatile fission products, including the β -emitters zirconium-95 (^{95}Zr), niobium-95 (^{95}Nb), ruthenium-103 (^{103}Ru), ^{106}Ru , cerium-141 (^{141}Ce), and ^{144}Ce (3–8).

Accidental exposure to nuclear fuel particles can occur via inhalation, ingestion, or via direct skin contamination. Due to the poor water-solubility of actinide particles, such as uranium oxide (UO_2) and plutonium oxide (PuO_2) particles, and consequent-

ly a low intake of the particles in the body, the most important organs or tissues from the radiobiological point of view are the lungs, the gastrointestinal tract, and skin. Knowledge about the biokinetic properties of nuclear fuel particles, in addition to the knowledge about the biological effects of these unique radiation sources, is essential in risk assessment of the health effects of the fuel particles.

Exposure to insoluble radioactive particles often leads to an exposure situation where only a minor fraction of the target tissue or organ is irradiated due to a short range of α - and β -irradiation (from a few microns to a few millimeters). The biological effects of nonuniform radiation exposure compared to uniform radiation exposure have been investigated in a number of theoretical and experimental studies for nearly three decades. The so-called “hot particle hypothesis” is based on the assumption that a nonuniformly distributed radiation dose is more carcinogenic than an equal radiation dose delivered uniformly to the same organ or tissue (9,10). The hypothesis was originally based on the effects of α -radiation. This hypothesis has repeatedly been refuted by many theoretical and experimental studies (11–15). As a consequence of the Chernobyl power plant accident, several theoretical and experimental studies coordinated by the International Atomic Energy Agency were initiated to study possible health hazards associated with the exposure to β -emitting hot particles (16). Recent experimental studies indicate that conventional dose risk

assessment models may underestimate the biological significance of β -emitting hot particles (17–21).

The primary aim of this overview is to describe the biokinetic properties of insoluble nuclear fuel compounds and the effects of nonuniform radiation exposure. First, we summarize data on hot particles, including sources, dosimetry, and human exposure. Second, data on the absorption, distribution and elimination of insoluble actinide particles in the gastrointestinal tract and respiratory tract, with special reference to insoluble UO_2 and PuO_2 particles, and nonvolatile, long-lived β -emitters Zr, Nb, Ru, and Ce are presented. Finally, we discuss short- and long-term biological effects of nonuniform α - and β -irradiation on the gastrointestinal tract, lungs, and skin.

Hot Particles

Sources

A hot particle is defined [applied to skin according to the National Council on Radiation Protection (14)] as a discrete radioactive fragment with a high specific activity (up to millions of Becquerels), insoluble in water, and not larger than approximately 1 mm in any dimension. Hot particles emit α -radiation, β -radiation, or β/γ -radiation. Natural uranium contains 0.7% of the fissionable uranium isotope ^{235}U (22). This natural isotope of uranium is currently the primary fuel used in nuclear power plants. Other fissionable nuclear fuels are ^{239}Pu and ^{233}U .

Both pressurized water reactors and boiling water reactors can cause hot particle contamination in the nuclear power plant environment (23). The particles usually contain activation products, such as ^{60}Co , or fission products of uranium. Activation product particles originate mainly from the high-cobalt stellite used in valve seats. Fission product particles are mainly released after failures in the nuclear fuel processes. The radioactivity of the ^{60}Co particles ranges from 40 Bq to 20 MBq with size range between a few microns and several millimeters. The radioactivity of fission

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products containing particles ranges from 40 Bq to 400 kBq with the same size range (24). In the United States, after examination of 61 nuclear power stations, 44 high-activity hot particles were found (25). The particles were both activation (metallic particles) containing mainly ^{60}Co with a size range from several microns to several millimeters, activities from 37 Bq to 37 MBq, and fission and fuel activation products with sizes and activities nearly of the same order. Mandjukov et al. (26) also found high-activity hot particles (85% activation, 15% fuel fragments) in the Kozloduy nuclear power plant in Bulgaria in 1992.

Hot particles containing α -emitters have been observed in the effluent from nuclear fuel reprocessing plants. For example, the effluent from the Sellafield reprocessing plant in the UK (27) has been found to contain small quantities of the α -emitting transuranium elements neptunium (Np), Pu, americium (Am), and curium (Cm) (28). Similar particles have been found in environmental samples taken near the plant.

The most important anthropogenic source for environmental radiation is nuclear weapons testing in the atmosphere (27). Carbon-14 is the main contributor to the dose, i.e., 2.6 mSv to the population in the north temperate zone, whereas the dose from fission products and plutonium is only 0.6 mSv (27). β -emitting hot particles isolated in the fallout of nuclear weapon tests had a mean geometric diameter of about 4 μm and a total activity up to 100 Bq. The main part of the particles contained the following components: $^{95}\text{Zr}/^{95}\text{Nb}$, molybdenum-99 (^{99}Mo), ^{131}I , tellurium-132 (^{132}Te)/ ^{132}I , barium-140 (^{140}Ba)/lanthanum (^{140}La), ^{141}Ce , and neodymium (^{147}Nd) (29).

Nuclear fallout from nuclear reactor accidents can contain both volatile, such as ^{137}Cs and ^{131}I , and nonvolatile fission products of uranium. The Chernobyl fallout in 1986 contained all nonvolatile fission products, including the β -emitters ^{95}Zr , ^{95}Nb , ^{103}Ru , ^{106}Ru , ^{141}Ce , and ^{144}Ce attached to uranium matrix (Table 1) (3–6). The total release was estimated to 290 PBq. About 50% of the releases were cesium isotopes, and 43% were nonvolatile fission products, whereas only 1.8% of the fallout was composed of plutonium isotopes (27). Hot particles in the Chernobyl fallout had a geometric diameter ranging from a few microns (Finland) to about 100 μm (Kiev). The total activity of the particles varied between about 30 Bq (average activity 130 Bq in Finland) (5,6) to over 1000 kBq (Poland) (8). Hot particles were also observed in the fallout from a nuclear

incident in 1992 at the power plant in Sosnovyi Bor, Russia (30). Gases and a small amount of cerium and zirconium isotopes containing nuclear fuel particles were identified in the surface air in Finland.

Dosimetry

An α -active hot particle emits radiation which only penetrates up to 100 μm in a biological tissue. For example, the absorbed dose rate in a simulated tissue-equivalent object at the distance of 10 μm from a 1 Bq ^{241}Am source (average α -energy, 5.4 MeV) is about 70 Gy/hr, whereas at the distance of 40 μm , it decreases to about 2 Gy/hr (31). The radiation dose in the immediate vicinity of the α -active particle is very high and would be expected to kill most of the cells exposed to the radiation.

The range of a β -radiation in a biological tissue can be in the order of a few millimeters depending on the β -energy. A β -emitting hot particle creates a dose gradient around it, causing cell death near the particle. The cells around the lethal zone obtain a sublethal dose, which does not kill the cells but is large enough to cause a random, malignant transformation (17–21). In Figure 1, a dosimetric model for a hot particle containing 1000 Bq of ^{106}Ru or ^{144}Ce is shown. For example, at the distance of 1 mm from the particle, the radiation dose rate is 0.01 Gy/hr, and at the distance of 0.2 mm, the dose rate is about 1 Gy/hr (5). Pöllänen and Toivonen (32) have calculated skin doses from large uranium fuel particles. The nuclide composition of the particles was estimated from the inventory of the Chernobyl reactor. For example, a uranium nuclear fuel particle of size 40 μm , deposited on the skin, can cause a dose of 1.6 Gy/cm². Hofmann et al. (33) calculated radiation doses and lung cancer risk for a hot particle composed entirely of ^{103}Ru . The authors concluded that in the immediate vicinity of a particle the doses are so high that all cells are killed and no tumors will arise. At intermediate distances, the probability for lung cancer induction exhibits a distinct maximum. According to the ICRP (34), inhalation of a 300 Bq (geometric diameter 1 μm) ^{103}Ru hot particle results in an average lung dose of 3.2×10^{-2} mGy/year. Burkart (35) concluded that the limited knowledge on the biological response of affected tissue and the limited experimental and epidemiological database for β -active hot particles requires additional information to elucidate the main characteristics of lung irradiation by hot particles.

The hot particle hypothesis was proposed by Geesaman (9) and Tamplin and Cochran (10). It implied that highly nonuniform radiation, for example on the skin or lungs,

Table 1. Physical data of nonvolatile fission products in an average hot particle (activity 130 Bq, aerodynamic size 10 μm) found following the Chernobyl fallout in Finland (6)

Radionuclide	Physical $t_{1/2}$ (days)	Activity (Bq)	Average β -energy (MeV)
Cerium-144	285	21.5	1.208 ^a
Cerium-141	32	26.7	0.144
Ruthenium-103	39	23.2	0.062
Ruthenium-106	368	5.42	1.415 ^b
Zirconium-95	64	27.5	0.115
Niobium-95	35	25.8	0.046

^aDaughter nuclide ^{144}Pr .

^bDaughter nuclide ^{106}Rh .

might be five orders of magnitude more harmful than uniform radiation. Most of the theoretical (12,14,15) and experimental studies (see Table 3) have refuted the hot particle hypothesis. However, we have observed that hot particle-induced carcinogenesis is associated with specific biological mechanisms that cannot be explained by mathematical modeling (17–21).

Human Exposure

Occupational exposure. Within nuclear power plants, hot particles may be attached to the workers due to electrical charges inherent in the plastic protective clothing worn by nuclear power plant workers (23). A high-activity hot particle can cause considerable local skin doses to exposed employees (25). Hot particles can also deposit on conjunctival tissue of workers, such as in the eye (36). Fuel cladding failure events may increase radiation exposure rates by an estimated 540% in some areas of the nuclear power plant during routine operations (37).

McInroy et al. (38) have reported a whole-body distribution of ^{239}Pu in an occupationally exposed worker. The worker was involved in operations with plutonium exposure from 1945 to 1982, approximately 10.5 months before his death. At the time of death the body contained 246 Bq of ^{239}Pu , of which 52.8% was found in the lungs and associated lymph nodes. The remaining 47.2% was mostly in the skeleton (44%), the liver (42%), with the remainder (14%) in the rest of the body. Studies on the 42-year follow-up of 26 Manhattan Project plutonium workers estimated that the plutonium depositions, including lung burdens, range from 52 to 3180 Bq with a median value of 500 Bq (39).

Health effects of α -active hot ^{239}Pu particles have been investigated in a few epidemiologic studies (39,41–44). The exposed populations have either been workers in nuclear weapon facilities or workers

accidentally exposed. The results have not shown any excess mortality or cancer incidence among the exposed persons.

Chernobyl fallout. Particulate fallout from Chernobyl extended over 1000 km from the accident site (3–5), exposing millions of people. In the vicinity of the Chernobyl nuclear power plant, a large number of people were exposed to both external γ -irradiation and highly penetrating β -irradiation from pulverized nuclear fuel, which was mainly deposited on the skin. The total number of the victims was 237; 140 persons were exposed to between 1 and 2 Gy, and 97 to between 2 and 8 Gy whole-body doses (45). All patients with total body doses higher than 4 Gy had skin burns. The β -emitters were deposited on the skin and clothes of the victims and caused severe burns (45,46) that often led to their deaths.

In more distant areas from the accident site exposure to hot particles occurred mainly via ingestion or inhalation. For example, the plutonium body contents of Gomel citizens in Russia, 4–5 years after the Chernobyl accident, were on average 3–4 times higher than the global levels (40). In Poland, the estimated annual intake of plutonium in the diet was 774 mBq/year in the first year after the Chernobyl accident and decreased to approximately 90 mBq/year in the sixth year (47). Lung doses in farmers living in the 30-km isolated zone around the power plant were estimated to be of the order of several milliSieverts during the first year after the accident (48). The number of hot particle-induced lung cancer cases for the Bulgarian population was estimated as four to six, or approximately 10% of the total number of lung cancer cases which are expected from external and internal irradiation after the Chernobyl accident (49). Balashazy et al. (7) estimated the lung cancer risk due to inhalation of Chernobyl-released hot particles to be less than 10^{-10} for individuals living in Budapest. In Finland, the epidemiological studies have focused on the fallout and incidence of childhood leukemia (50). However, human exposure to the Chernobyl hot particles has not been verified experimentally. In Finland as a whole, no increase in the incidence of childhood leukemia was observed from 1976 to 1992. However, some indication of an increase in the incidence of the disease was observed in the area with the highest exposure based on one or two extra cases per year.

Biokinetics of Nuclear Fuel Compounds in the Gastrointestinal Tract

Radionuclides can be ingested either by direct intake of contaminated food or water

or by swallowing inhaled material that has been cleared from the respiratory tract. Radionuclide absorption can occur from all segments of the gastrointestinal (GI) tract. The small intestine is generally the primary site of systemic uptake due to the large surface area of villus. Water-insoluble radionuclides that are not absorbed during GI transport or those that are first absorbed then subsequently secreted into the GI lumen and not reabsorbed are primarily excreted in feces. The excretion rate may vary greatly even within the same animal population because of unusual evacuation habits or unexplained physiological differences, for example (51).

Behavior of particulate material in the GI tract is affected by many factors. For example, large insoluble particles appear to pass through the tract more slowly than

much smaller particles ingested in solution (51). Solid particles may be absorbed via phagocytosis through Peyer's patches into lymph (52). Peyer's patches are lymphoid, follicular aggregates on the intestinal mucosa. Another mechanism of particle uptake is persorption (53), which means that as epithelial cells are sloughed off at the tip of the villus, a gap in the membrane is temporarily created, allowing entry of materials that are not membrane permeable. There is evidence for and against the persorption hypothesis (54). A third mechanism for particle transport is epithelial membrane damage. Absorption of particles can be enhanced after exposure to certain chemicals (52).

Actinides

Human data show that the actinide elements thorium (Th), Np, Pu, Am, and Cm

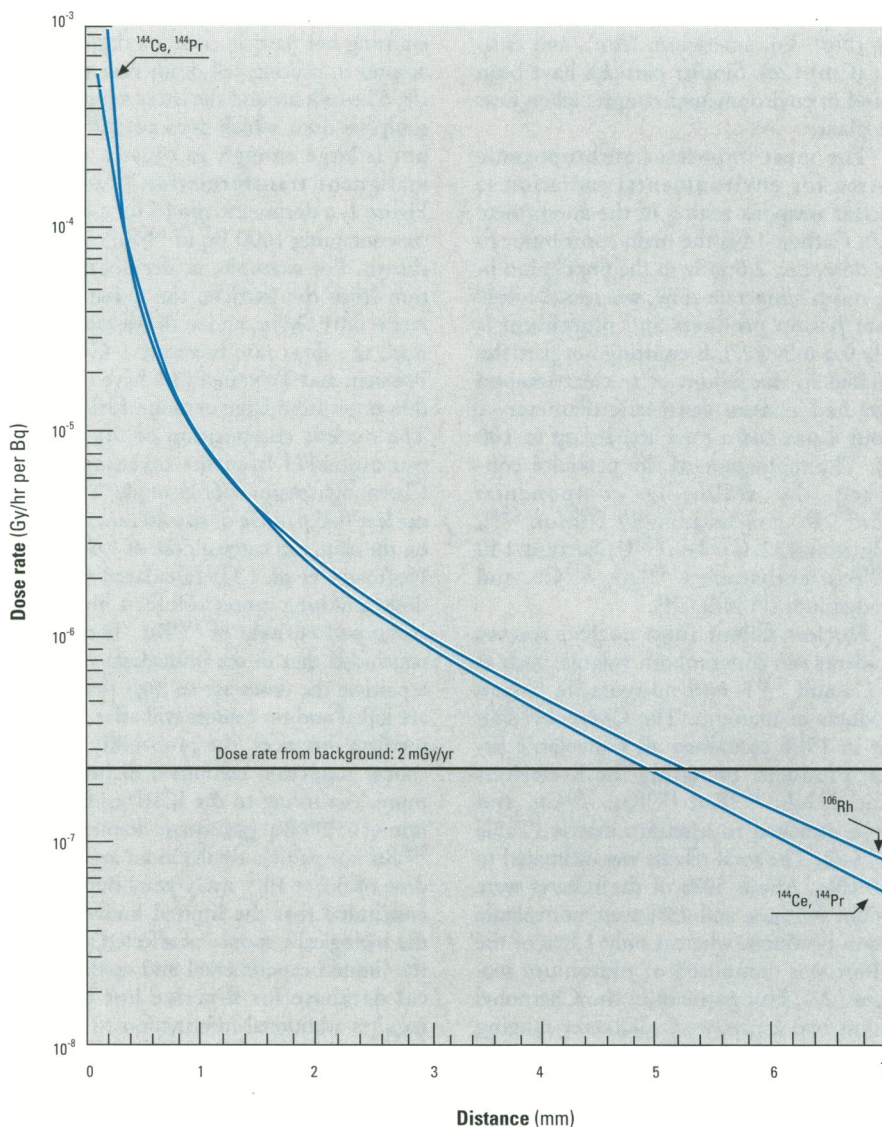


Figure 1. Radiation dose rate from a hot particle containing 1000 Bq of ruthenium-106 or cerium-144 and daughter nuclides rhodium-106 and praseodymium-144.

are absorbed poorly from the GI tract (55). The values for their fractional absorption are 2×10^{-4} (10^{-4} for Am). The gastrointestinal absorption of uranium is greater than that seen with the other actinides. This is consistent with its different solution chemistry. Uranium also behaves differently within the body, with a low intake in tissues other than bone. Uranium is primarily excreted via urine with associated retention in the kidneys (56). The average human GI absorption of U is most likely 1–2% and is probably independent of age or the mass of U ingested (57). Chemical and biological data for U and Pu are shown in Table 2.

In animal experiments, factors affecting the GI absorption of actinides, and particularly Pu, have been studied extensively. Values of fractional absorption in newborn animals, depending on the chemical form of the compound, vary between 10^{-2} and 3×10^{-5} (55). Values for adult animals are somewhat lower: between 10^{-3} and 3×10^{-5} . Oxides of Pu have very low absorption values, typically $<10^{-5}$. Fritsch et al. (58) have shown that absorption in neonatal rats is limited mainly to the first hours after ingestion, whereas in guinea pigs and primates, ingested Pu was retained in macrophages located beneath the intestinal epithelial cells. In neonatal primates, increased absorption appears to be due to uptake in distal epithelial cells. Higher values of absorption of many elements have been observed in fasted animals. Absorption of plutonium can be increased by an order of magnitude in fasted animals (59). This is presumably due to decreases in concentration of binding ligands which normally act as direct competitors for absorption.

Fractional absorption of U in hamsters, rabbits, dogs, and baboons is in the range of 3×10^{-3} to 2×10^{-2} , i.e., somewhat lower than for humans (57). Absorption values for rats are usually lower; values as low as 4×10^{-4} have been reported. The normal U content of a reference man is about 38 μ g, of which 66% is found in the skeleton (57). The natural U concentration in the human kidney (0.3% of the total body burden) appears to be about twice

that in the liver. When U is injected subcutaneously or intravenously, accumulation primarily occurs in the kidneys or bones (56). Uranium competes with calcium for sites of deposition. Neutron-induced autoradiographs of retained U in human bones show that under equilibrium conditions it is diffusively distributed throughout the bone volume (57). Uranium dioxide, UO_2 , with a melting point of $2078 \pm 20^\circ\text{C}$, is water-insoluble but soluble in HNO_3 and concentrated H_2SO_4 (60). The rate of dissolution of UO_2 in acids depends on the particle size, acid concentration, and temperature (61). Hodge and co-workers [see Yuile (56)] conducted 1- and 2-year feeding experiments in rats and observed that UO_2 was not absorbed by the GI tract. The chemical analyses showed no increase in the U content in the kidneys or bone.

Fission Products

Zr, Nb, and Ru belong to the transition metals and Ce to the inner transition metals (also called lanthanides or rare earths). These metals are water-insoluble in their dioxide form (60). Several experiments have been performed to study GI absorption of these uranium fission products in laboratory animals (34,62). The chemical and biological characteristics of these nuclides are shown in Table 2. The generally accepted values of fractional absorption for Zr, Nb, and Ce are less than 10^{-4} and 3×10^{-2} for Ru. The values are based on the studies with single nuclides in ion salts (e.g., chlorides, oxalates, and nitrates) (34). GI absorption of ^{95}Nb oxalate in the mouse, rat, and monkey is approximately 1% (63). In young rats, the whole body retention of ^{141}Ce nitrate is less than 0.04%, and absorption of various salts of $^{95}\text{Zr}/^{95}\text{Nb}$ is approximately 0.8% (64). In miniature swine, a whole-body retention of ^{144}Ce chloride of less than 0.01% has been reported (65). GI absorption of ^{95}Nb citrate in guinea pigs has been estimated as 0.8% (66).

A few studies have shown that whole-body retention of ^{95}Zr , ^{95}Nb , ^{141}Ce , and ^{144}Ce is significantly higher in suckling than in adult rats (67–69). The absorption

can be 10–100 times higher in neonates. This relative increase in absorption is probably due to retention of the radionuclides in the intestine where pinocytosis is more active in younger animals. For example, insoluble radionuclides such as cerium and niobium are readily taken up by the intestinal cells in suckling rats and are apparently immobilized in these cells and are cleared from the body only when the cells have migrated up to the villi and have been sloughed into the intestinal lumen (68). Increased absorption of ingested radionuclides in neonates is a general phenomenon (66) that is observed immediately after birth, followed generally by a progressive reduction over the suckling period (70). The absorption appears to be non-specific due to a greater permeability of the immature intestine for different elements and range of molecular species. This phenomenon may be related to the specific uptake of immunoglobulins from milk, which continues to a reduced extent after “closure” of the intestine to the transfer of these molecules (71). Intestinal retention of ^{95}Nb citrate in newborn guinea pigs is low, unlike retention in other species (66), but consistent with observations of the retention of actinide elements in this species (71). In the guinea pig, as in humans, this “closure” occurs either before or shortly after birth; maternal immunoglobulins are transferred cross-placentally to the fetus, and the mechanism of intestinal uptake from milk does not operate (72). Fasting results in a 75% increase in niobium absorption in guinea pigs (fasting 24 hr and 2 hr after the administration) (66).

Distribution studies with ion salts of ^{95}Zr , ^{95}Nb , ^{103}Ru , and ^{144}Ce in different animals species have shown that these radionuclides are primarily deposited in the bone both after oral and intravenous administration (63,69,73). Some uptake also occurs in the liver, kidney, spleen, and testis. Ruthenium, however, does not accumulate as strongly in bone as other radionuclides (73).

The fission products have entirely different biokinetic properties when administered in particulate form. Lang and Raunemaa (74) studied the behavior of simulated nuclear fuel particles in the GI tract of the rat. Whole-body autoradiography and γ -spectrometric tissue analyses showed no absorption of ^{141}Ce , ^{144}Ce , ^{103}Ru , ^{95}Zr , or ^{95}Nb from the GI tract. None of the radionuclides could be detected in the liver, kidney, muscle, bone, brain, blood, or urine. Approximately 98% of the total radioactivity was excreted in feces within 3 days post-exposure. Intestinal

Table 2. Chemical and biological data of uranium, plutonium, and nonvolatile uranium fission products (60,63)

Element	Solubility in dioxide form	Fractional absorption by ingestion	Fractional absorption by inhalation	Biological $t_{1/2}$ (days), total body
Uranium	Insoluble in H_2O ; soluble in HNO_3 , conc. H_2SO_4	$<10^{-4}$	0.25	100
Plutonium	Insoluble in H_2O ; soluble in conc. H_2SO_4 , HNO_3 , HF	3×10^{-5}	0.25	6.5×10^4
Cerium	Insoluble in H_2O ; soluble in H_2SO_4 , HNO_3	$<10^{-4}$	0.25	563
Ruthenium	Insoluble in H_2O , alkali; soluble in fused alkali	0.03	0.27	7.3
Zirconium	Insoluble in H_2O ; soluble in H_2SO_4 , HF	$<10^{-4}$	0.25	450
Niobium	Insoluble in H_2O , alkali; slightly soluble in alkali	$<10^{-4}$	0.25	760

retention for ^{141}Ce , ^{144}Ce , ^{103}Ru , and ^{95}Zr at 1 day after administration was between 2 and 3%; for ^{95}Nb retention it was about 6%. These results indicated that UO_2 fission products must first be released from the matrix of particles prior to absorption of nuclides across the intestinal mucosa. This is also supported by the observations of Mirell and Blahd (75) who performed whole-body measurements of an American tour group who were exposed in Kiev to the initial Chernobyl reactor accident plume. They found that ingestion of particulate fission products (^{141}Ce , ^{144}Ce , ^{131}I , ^{103}Ru , ^{137}Cs , $^{95}\text{Zr/Nb}$) appeared to result in a relatively short element-independent retention. Consequently, fission products in the fused particulate form renders them virtually inert in metabolic terms and the radionuclides are not metabolized along biological pathways characteristic for the elementary form (34). Ingestion of nuclear fuel particles does not lead to significant extraction of fission products from particles and their deposition into tissues where they may be retained for long periods of time.

Effects of Nuclear Fuel Compounds on the Gastrointestinal Tract

The toxicity of poorly absorbed, ingested radionuclides depends on the energy of the nuclide, the mass of the intestinal contents, and how long the nuclide remains in the gastrointestinal tract. The high rate of cell proliferation in the small intestine makes this tissue especially sensitive to ionizing radiation (76,77). The most radiosensitive cells in the intestine are the crypt cells. In humans, the crypt cells of the duodenum may lie 1.5 cm beneath the surface, whereas in the rat, the distance is approximately 0.02 cm. Consequently, the biological effects of poorly absorbed radionuclides depend on the type of radiation (i.e., the differences in ranges) the nuclides emit.

Sullivan et al. (78) exposed rats to the β -emitter yttrium-91 (^{91}Y) as the YCl_3 at 925 MBq/kg (dose to large intestine about 30 Gy) and to a suspension of $^{239}\text{PuO}_2$ (α -dose to the surface of the small intestine about 1000 Gy). Exposure to ^{91}Y caused severe damage to the cecum and colon, such as disruption of the crypt pattern, cystic dilation of the crypts, irregularity of the surface epithelium, cytoplasmic vacuolization, and edema and hyperemia of the submucosa. Plutonium α -particles induced only mild and superficial lesions confined to the cecum and colon. The authors concluded that ingested α -emitters did not induce acute toxicity, in contrast to β -emitters, because of the poor penetration of α -

irradiation to the radiosensitive crypt cells (78). In contrast, in neonatal rats, acute intestinal lesions leading to death were observed after gavage of ^{238}Pu (IV)-citrate (122 kBq per animal) (79). The neonatal rats might be more sensitive to α -irradiation because they have immature and poorly invaginated crypts compared to other mammalian species (80).

Studies with insoluble $^{238}\text{PuO}_2$ (81) and simulated nuclear fuel particles [depleted uranium in graphite matrix and strontium-89 chloride (51)] have shown that prolonged retention of particles in the intestine produces localized pathological lesions. In the pig intestine, $^{238}\text{PuO}_2$ particles caused villar-tip necrosis and inflammation in a 1-cm region surrounding the particles (81). In the rat, simulated nuclear fuel particles caused partial denudation of the epithelium and/or ulceration, and less severe damage with changes in the architectural structure in the villi and marked cellular atypia in the epithelial cells (51). Sikov et al. (51) concluded that the same amount of radiation administered uniformly in solution would not have caused serious damage. The potential for damage from an insoluble radioactive particle depends on the length of time the particle remains at a given point in its progress through the GI tract. Sullivan et al. (76) exposed suckling, weanling, and adult rats by gavage and adult beagle dogs by ingestion to high-energy (1.4 MeV average) ^{106}Ru -rhodium-106 (^{106}Rh) chloride solution. The LD_{50} values for suckling, weanling, and adult rats were 55,000, 666,000 and 333,000 kBq/kg, respectively. The newborn rats were most sensitive because of the absorption of the radionuclide into the mucosa of the lower small intestine where it can destroy that segment. In the same study the low-energy β -emitter promethium (^{147}Pm) caused death in rats by damaging the large bowel. The LD_{50} for ^{106}Ru - ^{106}Rh in dogs was about 129,500 kBq/kg. The signs of intestinal injury, duration of injury, and the probabilities of tissue repair were much different in the dog than in the rat (76). The midcolon and lower colon of dogs were usually denuded at focal sites rather than in widespread areas.

Biokinetics of Nuclear Fuel Compounds in the Respiratory Tract

Inhalation is considered the most likely route of accidental intake of radionuclides (82). Inhalation of particles can lead to deposition in the nasopharyngeal, tracheobronchial, and pulmonary regions of the respiratory tract. The extent of particle

deposition is a function of particle size, shape, and density of the aerosol, lung structure, and respiratory characteristics such as breathing rate, tidal volume, and expiratory reserve volume (62). It is also well documented that anatomic and physiological differences exist among experimental animals that may influence deposition patterns (83). For example, the simulation models for inhaled materials project an eightfold difference among rats, guinea pigs, dogs, and nonhuman primates in the lung concentration of particles per gram of lung after a 2-year chronic inhalation exposure to the same aerosol for 8 hr/day, 5 days/week (84). The largest lung accumulation would occur in guinea pigs, the smallest in rats. Deposited particles are taken up by endocytosis, either by phagocytosis or pinocytosis, during the first few hours after deposition. Particles are rapidly phagocytized by pulmonary alveolar macrophages or other phagocytic cells. Some particles may directly enter the alveolar interstitium by pinocytosis (84). There are also indications that the particles in the lungs are redistributed or aggregated due to macrophage migration and grouping (85), which may change the radiation dose or injury pattern. Water-insoluble radionuclides are absorbed in accordance with their dissolution rate, partition coefficient, and residence time in the respiratory tract (62).

The dominant routes for physical translocation of particles from the pulmonary region are the mucociliary escalator or the lung-associated lymph system, presumably phagocytosis. In addition to chemical dissolution of particles, physical forces may also influence the dissolution rate indirectly by altering the form of the particles and the surface area available for dissolution. Very small particles may also be translocated directly into the circulatory system (84). In addition, translocation of particles into the interstitium appears to be a function of the number of particles; i.e., the delivered dose and dose rate (86). Exhalation is a major elimination pathway for undeposited particles and gases.

Actinides

Oxides and hydroxides of actinides are water-insoluble compounds that have maximal retention half-times in the lungs of over 100 days (34). It has been shown that in the rat, inhaled particulate compounds of actinides become stored in phagolysosomes of alveolar macrophages (87). Rat alveolar macrophages possess the ability to phagocytize UO_2 particles despite the high toxicity the metal exerts on cell membranes (88). Soluble actinides, such as $^{241}\text{Am}(\text{OH})_3$, are solubilized within lysosomes, bind to cyto-

lic ferritin, and released from macrophages. The compounds can cross the alveolar membranes as transferrin or as low molecular weight forms. Insoluble UO_2 and PuO_2 particles remain within the lysosomes of alveolar macrophages and may damage the lysosomal membranes. The particles can thus also be observed free in the cytoplasm (87).

Leach et al. (89,90) exposed dogs, monkeys, and rats in a 5-year inhalation study to a natural uranium dioxide (UO_2) aerosol of approximately 1 μm mass median diameter at a mean concentration of 5 mg/m^3 . Biological half-times in the dog lung and tracheobronchial lymph nodes were 20 and 26 months, respectively. The analogous values for monkeys were 18 and 65 months, and for rats, 10 and 22 months respectively. Similar high lung-retention values in these animal species have been reported for mixed UO_2 and PuO_2 particles (91,92). Monkeys and rats clear plutonium and americium (in mixed oxide particles) from their lungs faster than dogs. The authors concluded that errors could result from using data from a single animal species to estimate inhalation risk to humans (89,90). LaBauve et al. (93) reported that in the rhesus monkey, the inhaled $^{239}\text{PuO}_2$ was retained in the body with an average effective half-life of 1000 days with some translocation to the pulmonary lymph nodes. Human data suggest that the biological half-time of UO_2 in the lung is between 500 and 1500 days (94).

Intratracheal instillation produces a much more nonuniform distribution of particles in the lungs than that seen after inhalation exposure (95–97). However, some aggregation of UO_2 particles seems to occur in the rat lung even after inhalation due to macrophage phagocytosis, probably as early as within 24 hr after the exposure (85). Similar observations have been made for PuO_2 particles in different animal species (98). Formation of large $^{239}\text{PuO}_2$ aggregates (>25 particles) may produce a mean dose rate as high as 120 Gy/day to the focal alveolar regions (99). The aggregation of actinide particles such as uranium dioxide is probably due to both the physical characteristics of the particles and active macrophage transport.

Relatively insoluble actinide particles which are retained in the lungs for long periods of time are slowly cleared mechanically by mucociliary action, swallowing, and excretion via the GI tract. Particles in the lower airways can also be transported to the tracheobronchial lymph nodes, or blood and further to various tissues. Studies on dogs have shown that the lung and lymph nodes associated with lymphatic drainage of the respiratory tract are the principal sites of

α -irradiation from inhaled $^{239}\text{PuO}_2$ (100). There is also evidence that various types of particles are not completely cleared from the large airways (101,102). For example, up to 0.7% of UO_2 particles injected in the rat trachea can be found in the trachea 14 days after exposure (101). The mechanism of retention in the tracheal wall is not clear, but probably consists of phagocytosis by epithelial cells.

Current studies reveal that the clearance half-time from the rat lung is 247 days for UO_2 particles with an aerodynamic diameter of 2.7–3.2 μm after a single exposure (103). Mixed (U,Pu) O_2 particles appear to have a shorter biological half-time in the rat lung compared to UO_2 particles but similar to PuO_2 particles (91,92,104,105) ranging from 60 to 100 days (87,102). The retention of these mixed oxide aerosols is not significantly influenced by particle shape or exposure method. In the baboon, lung retention of pure PuO_2 and mixed (U,Pu) O_2 was 56–80% of the initial pulmonary burden 1 year after a single inhalation exposure (92).

Dissolution of insoluble UO_2 and PuO_2 particles, which has been demonstrated both *in vitro* and *in vivo* (106), appears to be the dominant mechanical process in lung clearance. Uranium is dissolved more readily than Pu or Am in mixed UO_2 and PuO_2 particles, generally reflecting the physical nature of the UO_2 - PuO_2 matrix. Fragmentation of $^{238}\text{PuO}_2$ particles has a significant influence on the lung clearance of particles (105). This phenomenon probably reflects the increased surface area of particles which would increase their solubilization rate and direct transfer of nanometer-sized particles from the lungs to various tissues. Observations with PuO_2 (107) and CmO_2 (108) have shown that small particles, approximately 1 nm in diameter, are translocated intact from lungs to blood and urine. Cooper et al. (109) have shown that $^{233}\text{UO}_2$ particles <4 nm in diameter translocate from lungs to blood at the same rapid rate as $^{233}\text{UO}_2(\text{NO}_3)_2$. The authors suggested that small particles of UO_2 are oxidized during the inhalation procedure to UO_3 , which reacts with salt solutions in the lungs and forms the uranyl ion (109). The uranyl ions bind to the major pulmonary surfactant phosphatidylcholine and are translocated to blood. In plasma, approximately 50% of the ^{233}U is bound to transferrin, 25% to citrate, and 25% to bicarbonate.

Insoluble UO_2 particles retained in the lower airways are translocated poorly to other organs. Morris et al. (103) found 82% of the total body burden of enriched UO_2 in the rat lung at 720 days after expo-

sure. Ten percent of the activity was in the thoracic lymph nodes, 3.9% in bone, 3.2% in soft tissue, and 0.8% in the kidney. The values for other organs and tissues were below 0.1%. Similar observations have been made with mixed (U,Pu) O_2 particles (87). Only 1% of the initial alveolar deposit was found in the rat liver, spleen, or kidneys throughout the 200-day observation period. Lataillade et al. (92) reported that translocation of mixed UO_2 and PuO_2 from rat and monkey lung after a single inhalation exposure was less than 3% of the initial pulmonary burden. The translocation of Pu from the mixed oxide to the skeleton and liver was greater than that from the industrial PuO_2 . In mice, only about 0.5% of the inhaled $^{239}\text{PuO}_2$ is translocated to other organs (110).

Fission Products

The behavior of uranium nonvolatile fission products in the lungs has not been studied as extensively as their behavior in the GI tract. Chemical and biological characteristics of the nuclides are shown in Table 2. The mean biological half-time of ZrO_2 in the human lung has been estimated to be 224 days, and in the beagle dog the calculated value is 301 days (111). Thomas et al. (112) exposed mice to ^{95}Zr and ^{95}Nb in oxalic acid. The particles were generated at four different temperatures ranging from 100°C to 1100°C. Over 90% of the whole-body ^{95}Zr and ^{95}Nb was retained in the lungs at the higher temperatures (600° and 1100°C) and was cleared with a half-time of about 39 days. About 2–3% of sacrifice body burden was found in the bone. At the lower temperatures (100° and 250°C) the retention half-times were 61–62 days, and approximately 80% of the total body burden was found in the skeleton and 3% in the liver 120 days after inhalation. Different metabolism of the radionuclides was sometimes observed depending on the temperature of formation. Zirconium was translocated more readily to the bone than niobium. Inhaled $^{144}\text{CeO}_2$ particles are also translocated poorly from the lungs. Lundgren et al. (113) observed that, in the rat, 91% of the whole-body activity was found in the lungs 29 days after inhalation. The content in the skeleton was 1.0% at 270 days after inhalation, and 0.15% in the liver at 170 days after inhalation. Lang et al. (97) exposed rats to neutron-activated UO_2 particles, including the β -emitters ^{141}Ce , ^{144}Ce , ^{103}Ru , ^{95}Zr , and ^{95}Nb . At 1 day after intratracheal instillation, on average 78.1% of the total injected radioactivity was detected in the lungs. Only 0.7% of the activity was found in the trachea, and

the rest was in the gastrointestinal tract (8.3%) and feces (12.9%). One month after instillation, approximately 94% of the retained total body activity was in the lungs, and this decreased to 83% after 3 months. The activities in the liver, kidney, spleen, and bone were <1% of the retained total body activity. The fractional absorption in the liver and bone was significantly lower ($p < 0.05$) than expected (65,114), which was probably due to the administration of uranium fission products in particulate form. Clearance of uranium-matrix-associated fission products from the lungs is preferentially dependent on the physical characteristics of the particulate material, as previously described. Particle size is probably the most important factor in the translocation of water-insoluble particles from the lungs to the blood (105, 107–109).

Effects of Nuclear Fuel Compounds on the Lungs

Short-term Effects

Deposition of insoluble radioactive particles in the alveoli is associated with an elevated lung cancer risk due to the long retention of particles in the lower respiratory tract. However, the significance of the short-term effects of insoluble radioactive particles, such as inflammatory reactions, in the development of lung neoplasms is not well understood. High lung radiation doses are needed to cause early mortality in experimental animals. For example, studies on $^{239}\text{PuO}_2$ have shown that early death occurs in baboons and dogs after accumulation of lung doses between 20 and 100 Gy (115).

Alveolar macrophages represent the initial defense mechanism of the lungs for clearing particulate matter. Although the alveolar macrophages are not tumor precursor cells, they secrete various cell growth-related factors, such as interleukin-1, tumor necrosis factor, and leukotrienes (116). The high toxicity of UO_2 on macrophages depends on the interaction of the metal with phospholipids and proteins, resulting in alterations of membrane permeability in phagosomes. Successive events may lead to the leakage of hydrolytic enzymes which may in turn cause severe damage to the cytoplasmic organelles (88). At present, it is not known whether lysosomal membrane damage is due to chemical (by uranium) or radiological toxicity (87). Moores et al. (117) have shown that there is a significant depression in the number of mouse alveolar macrophages after exposure to $^{239}\text{PuO}_2$ at initially acquired doses greater than 20 Bq. Morgan and Talbot (116) reviewed diverse

effects of inhaled α -emitting actinides on mouse alveolar macrophages. For example, $^{239}\text{PuO}_2$ exposure appears to increase macrophage size, inhibit the mobility of macrophages, and enhance the phagocytic capacity. Cytoplasmic and lysosomal enzymes such as lactate dehydrogenase and α -glucuronidase are also activated by $^{239}\text{PuO}_2$. Induction of nuclear aberrations, particularly micronuclei, can be detected at doses as low as 1 Bq, corresponding to a cumulative radiation dose to lung of 50 mGy (118).

Recent data suggest that there are two distinct mechanisms involved in radiation-induced radiation damage: 1) classical pneumonitis, which ultimately leads to pulmonary fibrosis, is primarily due to radiation-induced local cytokine production confined on the field of irradiation; 2) sporadic radiation pneumonitis, which is an immunologically mediated process resulting in bilateral lympholytic alveolitis (119). Both animal experiments and human studies show that classical radiation pneumonitis has a threshold dose and a narrow dose-response curve with increased morbidity and mortality over a small dose range (119). For example, in rats, inhalation of high-fired $^{239}\text{PuO}_2$ (initial lung burden 3.9 kBq) leads to peribronchial particle aggregation, which increases with time and results in well-defined focal inflammatory lesions after 120 days (120). The exact mechanisms of radiation pneumonitis induced by insoluble radioactive particles are not fully understood. One possible mechanism is damage to type II cells, causing alterations in the cell differentiation and disturbances in the metabolism of surfactant phospholipids (121), or type II proliferation with failure to develop into type I cells (122). Taya et al. (123) have shown that significant cellular changes, particularly cell proliferation (mainly type II and Clara cells), occur early after exposure of mouse lung to $^{239}\text{PuO}_2$ at initial alveolar deposit of 500 Bq. However, the relevance of the results to the late carcinogenic effects of $^{239}\text{PuO}_2$ could not be verified because of the limited duration of the study.

Effects of insoluble, internally deposited radionuclides on the pulmonary clearance of inhaled bacteria have been reported in a few studies (124–126). For example, inhalation exposure to insoluble $^{144}\text{CeO}_2$ and $^{239}\text{PuO}_2$ particles reduced the pulmonary clearance of *Staphylococcus aureus* in mice (124). The authors suggested that direct radiation injury to the alveolar macrophage population was the likely cause of the reduced clearance (124). It has also been shown that inhaled ^{144}Ce in a relatively insoluble form results in

detectable changes in the pulmonary surfactant, important in the killing of bacteria by pulmonary macrophages (127). These studies indicated that insoluble radionuclides may decrease an animal's resistance to bacterial invasion of the lungs and increase the risk for pneumonitis. Studies with simulated nuclear fuel particles (neutron-activated UO_2) show that particles induce local inflammatory changes at the cumulative lung doses of 170, 230, 400, and 550 mSv (97). As a short-term effect, the particles also appeared to modulate the cytochrome P450 enzyme activities, which in turn may affect the metabolism and effects of xenobiotics and chemical carcinogens (128).

Pulmonary Fibrosis

Fibrosis-associated changes apparently have their origin in the pneumonitic phase (35,119,129). At the light microscope level, fibrosis is defined as an increase of connective tissue fibers as a result of inadequate regeneration of parenchyma. Collagen accumulation may alter the normal ratio of type I (coarse fibered) to type III (meshwork) collagen. Cellular disturbances play an important role in the alterations of the alveolar structure involving cell death on the endothelial and epithelial sides of the basement membrane and damage to the immune-competent cells (130). Biochemical and histological evidence of fibrosis may be detected as early as 2 months after radiation exposure (129). Gas transfer is impaired by fibrosis as a result of thickening of alveolar-capillary barriers and reduction in the effective surface area. Recent studies have shown that irradiation induces gene transcription and results in the induction and release of proinflammatory cytokines and fibroblast mitogens, which ultimately results in pulmonary fibrosis (119). Ionizing radiation may induce synthesis of various inflammatory gene products, such as EGR1 (131), platelet-derived growth factor (132), and necrosis factors (133).

Studies with insoluble, fused aluminosilicate particles carrying ^{90}Y have demonstrated a typical pneumonitic phase in beagle dogs and lung function changes typical of pneumonitis and fibrosis (134). Inhalation of ^{144}Ce fused clay particles have shown an early increase in ultrafiltrable hydroxyproline in the lungs of beagle dogs (135), suggesting an increase in collagen degradation, preceding the synthetic phase of more soluble collagen. Beagle dogs may have signs of restrictive lung disease 1–5 years after exposure by inhalation to $^{239}\text{PuO}_2$ at initial pulmonary burdens of 330–4100 kBq/kg of body mass (136).

LaBauve et al. (93) observed marked alterations in respiratory function in a Rhesus monkey 30 days before its death from pulmonary fibrosis 990 days after inhalation exposure to $^{239}\text{PuO}_2$ (estimated initial lung burden 37000 Bq). Exposure of rats to high-fired $^{239}\text{PuO}_2$ (initial lung burden 3.9 kBq) resulted in fibrotic lesions 180 days after inhalation (120). Some studies with soluble and insoluble ^{239}Pu particles have shown that the metabolism of collagen, glycosaminoglycans, and lipids in laboratory animals are all shifted toward enhanced synthesis (129). McAnulty et al. (137) observed dramatic increases in both synthesis and degradation rates of collagen in the mouse lung after exposure to $^{239}\text{PuO}_2$, suggesting an extensive remodeling of the lung connective tissue matrix during development of fibrosis. Preexisting, bleomycin-induced pulmonary fibrosis has been shown to decrease significantly the clearance of $^{239}\text{PuO}_2$ in the rat lung (138). However, the risk of lung tumors in rats with or without existing pulmonary fibrosis were similar. Diel et al. (139) exposed beagle dogs to $^{239}\text{PuO}_2$ once (accumulated doses of 23 ± 8 Gy) or repeatedly (22 ± 5 Gy during 7–10 semiannual exposures). Clearance of plutonium from the lungs of dogs exposed repeatedly was slower than in the dogs exposed once. Pulmonary fibrosis accounted for 72% of the radiation-related deaths in the single-exposure study and 87% in the repeated-exposure study. The remaining dogs died from pulmonary cancer. The dose rate did not appear to be an important factor in predicting death from radiation pneumonitis or pulmonary fibrosis.

Pulmonary Cancer

Tumors in the lung as a direct consequence of inhalation or instillation of radioactive materials are easily demonstrated in animals. However, in rodents, spontaneous or radiation-induced tumors normally occur in the alveolar region, whereas in man they are located in the bronchiolar region (129). Studies on Japanese A-bomb survivors and American uranium miners have shown that radiation-induced lung cancers appeared more likely to be of small-cell subtype and less likely to be adenocarcinomas (140). The review of lung cancer cases revealed further that the proportion of squamous cell cancer was positively related to smoking history in both populations. Absolute radiogenic risks of radiation-induced lung cancers are similar for both sexes, although baseline lung cancer risks are much higher than they are for females (141). Other factors important in risk assessment of the effects of radioactive particles in the lungs involve the particle size, chemical and physical form of the particles, the type of radioactive emission, the physical half-life of the radionuclide and its biological half-time in the lungs. Animal experiments indicate that prolongation of β -irradiation of the lung from a period of days to years reduces its tumorigenic effectiveness by a factor of about 3, and that chronic α -irradiation of the lung from inhaled $^{239}\text{PuO}_2$ is 10 to 20 times more carcinogenic than chronic β -irradiation (141). Burkart (35) has stated that both from the point of view of contracted dose and radiosensitivity, the human lung is the most critical organ for

late somatic health effects from exposure to ionizing radiation in our environment.

Alpha-emitters

Several animal studies have been performed to study long-term effects of insoluble α -emitters. Leach et al. (89,90) studied long-term effects of natural UO_2 particles in the monkey, dog, and rat. Inhalation of 1 μm mass medium diameter particles at a mean concentration of 5 mg/m^3 , (6 hr per day, 5 days per week) did not cause serious injury in animals during the 5-year exposure. In the following post-exposure period, malignant tumors developed in 31% of the dogs 2–6 years after the exposure. The effects of inhaled $^{238}\text{Pu}/^{239}\text{Pu}$ dioxides have been studied in rats (104,142), Syrian hamsters (143), and mice (144). These studies demonstrated, except for studies in mice, that prolonged inhalation of insoluble α -emitters does not enhance pulmonary carcinogenesis as compared to a single exposure. Both $^{238}\text{PuO}_2$ and $^{239}\text{PuO}_2$ have been shown to cause malignant lung tumors in dogs (139,145,170–173). Diel et al. (139) exposed beagle dogs to $^{239}\text{PuO}_2$ once and repeatedly (7–10 semiannual doses) to 22–23 Gy lung doses by inhalation. In the single exposure, 28% of the dogs died with pulmonary cancer, whereas in the repeated exposure the death rate was 13%. Gillett et al. (146) also observed primary liver tumors in beagle dogs exposed by inhalation to $^{239}\text{PuO}_2$. In baboons, $^{239}\text{PuO}_2$ particles caused slightly differentiated lung carcinoma and bronchogenic adenoma (115). Hahn et al. (147) also observed fibrosarcoma in the lung of a rhesus monkey after

Table 3. Summary of selected experimental studies supporting or refuting the hot particle theory

Species	Experimental design	Tumor incidence	Reference
Sprague-Dawley rats, male	Single external β -irradiation of skin with ^{91}Y -source; grid, sieve, and uniform exposure	Markedly delayed after grid and sieve nonuniform radiation exposure compared with uniform exposure	Albert et al., 1967 (180)
CBA/H mice, female	Single external β -irradiation of skin with ^{204}Tl -source; irradiation over one or two zones	Proportional to the area of irradiated skin	Hulse, 1967 (181); Hulse et al., 1983 (182); Papworth and Hulse, 1983 (183)
SAS/4 mice	Single external β -irradiation of skin with ^{170}Tm source; uniform and arrays of nonuniform 8 or 32 sources	30% Reduction by the 32-point array at low doses; an order-of-magnitude reduction by the 8-point source at low doses	Williams et al., 1986 (184); Charles et al., 1988 (185)
Sprague-Dawley SPF rats	Inhalation of uniformly distributed, soluble $^{244}\text{Cm}(\text{N-O}_3)_3$ and particulate $^{239}\text{PuO}_2$ (hot particle model)	Uniformly distributed $^{244}\text{Cm}(\text{N-O}_3)_3$ up to 5 times more toxic than $^{239}\text{PuO}_2$	Lafuma et al., 1975 (152)
Syrian golden hamsters	Repeated intratracheal instillation of α -active ^{210}Po absorbed onto Fe_2O_3 particles or in 0.9% NaCl solution (more uniform distribution)	Incidence nearly similar in both experiments	Little and O'Toole, 1974 (11)
C3H 10T1/2 cells	Irradiation of cells with Chernobyl-released and simulated nuclear fuel particles	Malignant transformation in each cell culture; expected incidence 0%	Servomaa and Rytömaa 1989,1990 (17,18); Servomaa et al., 1992 (19)
Hairless mice	Implantation of simulated nuclear fuel particles under the dorsal skin	Incidence about 10% in exposed sites; expected incidence 0%	Lang et al., 1993 (20); Leszczynski et al., 1994 (21)

inhalation of $^{239}\text{PuO}_2$. Sanders and co-workers (99,148,149) exposed Wistar rats to $^{239}\text{PuO}_2$ aerosol. Survival was significantly reduced only in rats with lung doses >30 Gy. Ninety-nine primary lung tumors were found out of the 2105 exposed animals, of which 92% were malignant and 80% carcinomas. The authors suggested that all types of malignant lung tumors exhibited a threshold at a lung dose >1 Gy (149). No significant difference was observed in nonpulmonary tumor location or type between control and exposed rats (148). Studies on plutonium-induced pulmonary neoplasms in the rat suggest that the alveolar epithelial surface may be more at risk for neoplastic transformation than the other histological types of proliferative foci (150). The majority of plutonium-induced proliferative epithelial lesions and neoplasms in the rat appear to originate from alveolar type II pneumocytes (151).

Little and O'Toole (11) studied the effects of nonhomogeneously and uniformly distributed ^{210}Po on the hamster lung. The average macroscopic dose to the lung was about 200 Sv. Tumor incidence was higher in the animals exposed to ^{210}Po in solution than in animals exposed to ^{210}Po bound to Fe_2O_3 particles with nonuniform dose distribution (see also Table 3). Nonuniform irradiation also resulted in longer latency periods. Lafuma et al. (152) exposed rats to soluble, uniformly distributed $^{244}\text{Cm}(\text{NO}_3)_3$ and insoluble $^{239}\text{PuO}_2$, which served as a model for hot particles. Uniformly distributed $^{244}\text{Cm}(\text{NO}_3)_3$ was up to five times more toxic than particulate $^{239}\text{PuO}_2$ (Table 3). Most inhalation studies with relatively insoluble α -emitters appear to produce lung cancers in rats, mice, and dogs at initially acquired doses above 0.04 Mbq/kg, with peak incidences in the range of 0.6–3.7 MBq/kg (129). Recent studies by Lundgren et al. (153) have shown that the relative biological effectiveness in rats of the α -particle doses to the lungs from inhaled $^{239}\text{PuO}_2$ relative to β -particle doses to the lungs from inhaled $^{144}\text{CeO}_2$ is 21 ± 3 .

Beta-emitters

Most experiments with β -emitters have involved studies with compounds of ^{144}Ce in rats (113,154,155), mice (156,157), and Syrian hamsters (158). In hamsters and rats, the incidences of primary lung tumors were more dependent on the cumulative β -radiation doses to the lungs than the radiation dose-rate pattern. For example, in rats, a mean life time dose of 250 Gy resulted in 91.9% incidence of malignant lung tumors, whereas a 50 Gy dose caused 27% tumor incidence (137). The most frequently occurring malignant tumors were adeno-

carcinomas and squamous cell carcinomas. Even neutron-activated UO_2 particles induce benign or malignant tumors in rat lung at cumulative 24-month lung doses of 0.4–0.66 Gy (128,159). Squamous cell carcinoma and adenocarcinoma are the most frequently occurring tumors in the rat lung after exposure to β -irradiation (155,160). The incidence of primary lung tumors in rats is a slow process and appears to be related to the cumulative β -radiation dose. In mice, protraction of the absorbed dose resulted in a sparing from the life-shortening effects of ^{144}Ce pulmonary irradiation (156). Seventy-day-old mice were more sensitive to development of late-occurring effects of inhaled $^{144}\text{CeO}_2$ than 260- and 450-day-old mice. Experiments on beagle dogs have shown that protracted irradiation of the lungs with ^{144}Ce or ^{90}Sr result in a relatively high radiation dose and produce more total lung tumors but fewer lung tumors per Gray than less protracted irradiation with ^{90}Y and ^{91}Y (161). The carcinomas included adenocarcinomas, squamous cell carcinomas, or combinations of these types. Hemangiosarcomas were induced in animals that were exposed to ^{144}Ce and ^{90}Sr but were not found after ^{90}Y or ^{91}Y exposures; this tumor type was not even found in earlier inhalation exposure of beagle dogs to $^{239}\text{PuO}_2$ (162). Boecker et al. (163) exposed beagle dogs once, briefly, by inhalation, to the β -emitter ^{91}Y or to the α -emitter $^{239}\text{PuO}_2$. $^{239}\text{PuO}_2$ was more effective in producing lung cancer than was ^{91}Y ; risk coefficients for $^{239}\text{Pu}/^{91}\text{Y}$ ranged from 10 to 18.

Molecular Mechanisms of Lung Carcinogenesis Induced by Insoluble Nuclear Fuel Particles

The conversion of lung cells from normal to malignant involves a series of molecular changes, including the inactivation of tumor suppressor genes, the activation of dominant oncogenes, or other disturbances in normal cellular processes (164). The p53 tumor-suppressor gene appears to have a central role even in radiation-induced neoplasms of the lung. For example, p53 mutations have been observed in lung tumors of miners exposed to radon (165,166) and in lung cancers from radiation-exposed and nonexposed atomic-bomb survivors from Hiroshima (167).

Molecular changes in the lungs associated with radiation carcinogenesis after exposure to insoluble nuclear fuel particles are not well understood. However, the p53 tumor suppressor gene appears to have a central role even in radiation lung carcinogenesis induced by insoluble nuclear fuel particles. We observed both overexpression

and mutations in the p53 gene in malignant tumors in the rat lung after exposure to neutron-activated UO_2 particles (159). The base change was identical in each case. Transition of C:G to T:A in the CG dinucleotide as a result of low-LET radiation may be similar to CC to TT double-base change in UV-associated skin cancer (168,169) or AGG to ATG transversion in high-LET-radiation related lung cancer (166).

Some studies have also been performed to investigate molecular mechanisms in the lungs after exposure to $^{239}\text{PuO}_2$. The expression of epidermal growth factor receptor (EGFR) was detected in plutonium-induced lung neoplasms in dogs (170). Forty-seven percent of lung tumors expressed EGFR; however, the expression was not correlated with tumor etiology (e.g., spontaneous versus radiation-induced), but did correlate with specific histologic phenotypes. The same group (171) observed an increased (59%) expression of transforming growth factor- α (TGF- α) in plutonium-induced lung neoplasms in the dog. Twenty-seven percent (32/117) of radiation-induced proliferative epithelial foci expressed TGF- α , and many of these foci (8/32) expressed both EGFR and TGF- α . The results indicated that the foci exhibiting increased expression of the growth factor or its receptor represented preneoplastic lesions which were at greater risk for progression to neoplasia. Even a significant increase in EGFR binding has been observed in plutonium-induced dog lung tumors (172). Davila et al. (173) have also observed severe depression of immune response in tumor-bearing beagle dogs which had been exposed to $^{239}\text{PuO}_2$. Overexpression of TGF- α and EGFR have also been observed in plutonium-induced malignant tumors in rat (174). These data suggested that increased amounts of TGF- α were early alterations in the progression of plutonium-induced squamous cell carcinoma, and the increases may occur in parallel with overexpression of the receptor for this growth factor.

Stegelmeier et al. (175) have also investigated molecular and genetic alterations of Ki-ras in preneoplastic foci and neoplasms in the lungs of rats that had inhaled $^{239}\text{PuO}_2$. Specific Ki-ras point mutations were present in 46% of the radiation-induced malignant neoplasms. Similar mutation frequencies were observed in radiation-induced adenomas and foci of alveolar epithelial hyperplasia, but no mutations were identified in normal lung tissue. The findings suggested that Ki-ras activation, not alterations in expression, is an early lesion associated with many radia-

tion-induced, proliferative pulmonary lesions and that this molecular alteration may be an important component of both radiation-induced and spontaneous pulmonary carcinogenesis in the rat.

Biological Effects of Nonuniform Radiation on the Skin

Acute Effects

The response of the skin to ionizing radiation is highly complex and depends to a large extent on the exposure conditions (176). The basic underlying pathogenic mechanisms following hot particle exposure appear to be different from classical radiation damage to skin. The primary lesion resulting from irradiation with hot particles is acute ulceration (176). The depth and size of the ulcer depends on the skin surface dose and the energy of the radiation from the particle. Before the development of an ulcer, a small pale, circular area with a slight bluish tinge can be detected, which is frequently surrounded by a halo of erythema. Within a few days of irradiation, pyknosis of nuclei of endothelial cells and fibroblasts can be seen in the papillary dermis, and within 5–7 days the papillary dermis is largely without cell nuclei. These changes result from the direct cell death of these cells in interphase after doses >100 Gy. Acutely produced ulcers of the skin tend to heal rapidly if they do not become infected, and the lesion leaves a small scar with the appearance of a small dimple (20,176).

The ED₅₀ (effective dose) values for acute ulceration from ⁹⁰Sr/⁹⁰Y and thallium-170 (¹⁷⁰Tm) particles <1 mm in diameter is about 250 Gy (177). Moist desquamation cannot be seen after hot particle irradiation, but late dermal atrophy may develop at doses below the threshold for ulcer formation (178). Lang et al. (20) exposed hairless and nude mice to neutron-activated UO₂ particles. Within the first two weeks, an ulcer (diameter 1–4 mm) with erythematous and thick edges developed. At about 3 weeks, the hyperplastic epidermis often had a papillomalike appearance. Histologically, a five- to sixfold increase in epidermal thickness was observed. Inflammatory and giant cells of foreign body type were seen in the dermis. It is currently believed (14,15) that the only type of hot particle-induced lesion of concern is acute ulceration or breakdown with subsequent infection leading to ulceration.

Carcinogenesis

Ionizing radiation is a complete carcinogen (i.e. initiator and promotor), in rodent skin

(13). In rats and mice, and in humans, the times between irradiation and appearance of tumors, as fractions of life span of the species, is similar. Protraction of radiation dose produces a reduction in its carcinogenicity in rats, whereas in mice no sparing effect has been observed. The human data support a significantly lower skin cancer incidence, at least two orders of magnitude lower than that in rodents (179). Some of this discrepancy may be because the human tumors are mostly basal cell carcinomas, whereas only a few radiation-induced cancers in the experimental animals are of this type.

Most of the long-term studies on skin carcinogenesis after hot particle exposure have refuted the hot particle theory (Table 3). Albert et al. (180) showed that the rat skin tumor yield after grid and sieve nonuniform radiation exposure was markedly delayed compared with uniform exposure. Hulse and colleagues (181–183) irradiated CBA mice with thallium-204 (²⁰⁴Tl) particles using 12 different surface doses (5.4–260 Gy) and 4 different dose rates (1.7–200 cGy/min). The average latent period for tumor formation was 7 months, and more than 70% of the tumors were of dermal origin, 30% epidermal, and more than 60% were malignant. The tumor yield was proportional to the area of skin irradiated (182). Williams and his colleagues (184,185) exposed 1200 SAS/4 mice to uniform ¹⁷⁰Tm-sources (8.6 cm²) and nonuniform ¹⁷⁰Tm sources, which were arrays of either 32 or 8 sources, each 2 mm in diameter, distributed over 8 cm². Average skin doses varied from 2–100 Gy. The nonuniform irradiation showed a 30% reduction in tumor incidence by the 32-point array at the lower mean doses compared with the response from uniform sources. The 8-point array showed an order-of-magnitude reduction in tumor incidence compared to uniform irradiation at low doses. Even national and international radiation protection organizations have stated their objection to the hot particle theory (14,15).

Our current observations (20,21) do not agree with the previously reported results. We exposed hairless and nude mice to neutron-activated UO₂ particles by implanting the particles under the skin, which permitted a continuous long-term exposure of the skin to hard β-irradiation. The results suggested that there was an excess of skin cancers in mice exposed to hot particles compared with the numbers estimated using a conventional, nonthreshold stochastic model of radiation-induced cancer (see Table 3). The results of the previous studies have undoubtedly been correct, but the conclusions have been too

generalized. The results in our studies showed further that any direct mathematical–statistical extrapolation is not always appropriate but requires judgmental evaluation of biological mechanisms.

Biological Mechanisms of Skin Carcinogenesis Induced by Hot Particles

Development of skin cancer has been shown to be associated with the activation of many genes, particularly oncogenes and tumor-suppressor genes. Current evidence indicates that carcinogenesis is a multistep process (186,187). Activation of *ras* (188) and *c-myc* oncogenes (188,189) has been observed in radiation-induced skin tumors in rats. Overexpression of *ras* oncogenes has been found in many preneoplastic tumors, suggesting that *ras* activation is often an early event in tumor formation (187). Biopsy studies have shown that in radiation-induced rat skin tumors, *c-myc* functions as a late-stage progression-related oncogene (189). Physical parameters such as LET, dose, and dose rate may also affect oncogene activation patterns (190).

Our observations (20,21) suggest that the development of hot-particle-induced skin cancer depends on a few essential cellular and molecular mechanisms. The development of a permanent wound is an essential step in the carcinogenesis induced by nonuniform β-irradiation. The wound acts as a promoter by stimulating the proliferation of surrounding mutated cells. The skin exposure to simulated nuclear fuel particles revealed further that expression of p53 tumor-suppressor protein was frequent (28%) at the exposed sites (21). In some cases p53 protein was detected not only in the nucleus but also in the cytoplasm of the epithelial cells. The expression of the oncoproteins p62^{c-fos} and 21^{N-ras} was also markedly elevated in all the p53-expressing skin samples. The results showed that apparent carcinogenesis-related molecular changes occur frequently in the mouse skin well before the development of a distinct tumor, and probably even before premalignant changes can be detected by conventional histopathological analysis.

The key feature in carcinogenesis is that an agent can increase the incidence of cancer in one of two ways: it can specifically damage the DNA in a cell or increase the number of cell divisions, thereby providing a greater opportunity for (spontaneous) genetic errors during DNA replication (191). In hot particle exposure, both mechanisms are simultaneously involved and, possibly even more important in view of the multistage model of carcinogenesis, the number of cell divisions is increased in the

same cells in which specific radiation-induced DNA damage is most likely to occur. Our *in vivo* studies (20,21) directly support the general multistage model of carcinogenesis according to which the mechanism is based on genotoxic (DNA damage) and nongenotoxic (cell proliferation) effects. These observations are also supported by our *in vitro* experiments where C3H10T1/2 cells were exposed to Chernobyl-released and simulated nuclear fuel particles (17–19). Malignant foci developed in all cell cultures usually 2–4 mm from the radiation source. In addition, almost all the tested 11 oncogenes were activated by radiation, though in none of them was this change common.

Conclusions

Environmental releases of insoluble nuclear fuel particles may occur both in nuclear power plants in normal operation and following nuclear power plant accidents. The effects of hot particles on humans have been assessed in a few epidemiological and theoretical studies based on occupational exposure to PuO₂ particles and exposure to Chernobyl-released uranium particles. The results have so far been only speculative due to the lack of detailed and reliable data on the exposure. However, the biokinetics and biological effects of nuclear fuel compounds have been investigated in a number of experimental studies using various cellular systems and laboratory animals.

Ingestion of insoluble nuclear fuel compounds does not pose a serious radiological health problem. UO₂ and PuO₂ particles are not absorbed to any significant extent from the GI tract of experimental animals. Fission products ¹⁴⁴Ce, ¹⁴¹Ce, ¹⁰³Ru, ⁹⁵Zr, and ⁹⁵Nb are also absorbed poorly in their elementary form, whereas they are almost metabolically inert in the fused particulate form in the uranium matrix. However, in neonatal animals the absorption is higher. A slight retention of compounds may occur in the intestinal cells, but only extensive amounts of nuclear fuel material with prolonged retention in the GI tract may cause serious lesions in the radiosensitive cells crypt cells of the intestine.

Inhalation of insoluble nuclear fuel compounds induce both benign and malignant lung tumors in experimental animals. The elevated cancer risk is due to the long retention of particles in the lower respiratory tract. However, both intratracheal instillation and inhalation of insoluble nuclear fuel particles seems to lead to a nonuniform distribution of particles in the lungs and therefore complicates the assessment of the lung cancer risk based purely on the conventional dose calculations. Trans-

location of PuO₂ and UO₂ particles and fission products ¹⁴⁴Ce, ¹⁴¹Ce, ¹⁰³Ru, ⁹⁵Zr, ⁹⁵Nb in the particulate form from the lungs to other organs or tissues is poor.

The development of hot particle-induced cancer has been investigated in a number of experimental and theoretical studies. Most of the studies have suggested that nonuniform distribution of ionizing radiation is less carcinogenic than the same amount of radiation delivered uniformly to the same organ or tissue. However, current observations indicate that the development of a permanent wound is an essential step in carcinogenesis induced by nonuniform β -irradiation. This is also the primary lesion in the skin resulting from hot particle irradiation. The wound acts as a promoter by stimulating the proliferation of surrounding mutated cells. The experimental design in most of the studies has not allowed the development of a permanent wound, which in part may explain the obvious discrepancy between the results. In addition, the contradictory results can also be explained by the different effects of nonuniform α - and β -irradiation on biological material.

Exposure to insoluble nuclear fuel particles may induce various changes at the molecular level, which can be observed long before the development of a tumor. Overexpression and mutations of genes regulating cell proliferation and cell growth have been observed both *in vitro* and *in vivo*. The tumor-suppressor gene p53 may play a central role even in carcinogenesis induced by nonuniform radiation exposure.

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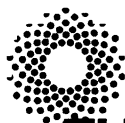
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THE AMERICAN SOCIETY FOR CELL BIOLOGY

Thirty-Fifth Annual Meeting
December 9-13, 1995
Washington Convention Center
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The thirty-fifth ASCB Annual Meeting will include symposia, mini symposia, poster sessions, special interest subgroup meetings, special lectures, workshops, and other events that reflect the eclectic nature of cell biology and the tremendous impact of cell biology on all aspects of biomedical research. Each facet of the program incorporates venues designed to increase interaction among scientists and the exchange of ideas among all participants.

EXHIBITS

The commercial exhibits will be open 9:00AM-4:00PM Sunday-Tuesday, December 10-12 and Wednesday, December 13 from 9:00AM-3:00PM. There will be approximately 450 exhibit booths, allowing registrants the opportunity to examine state-of-the-art products and services. The ASCB will provide complimentary refreshments each morning and afternoon in the exhibit hall.

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